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Single Case

Pityriasis Lichenoides et Varioliformis Acuta Developing during Pembrolizumab Treatment for Bladder Cancer

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Keywords

Pityriasis lichenoides et varioliformis acuta · irAE · Pembrolizumab · Anti-PD-1 · Granzyme B

Abstract

Introduction: Anti-PD-1 immunotherapies enhance T-cell responses against tumor cells by blocking the interaction between PD-1 and its ligand, PD-L1. While these therapies offer significant benefits in treating various malignancies, they can also lead to several immune-related adverse events (irAEs), most notably manifesting in the skin. Lichenoid reactions, eczema, and vitiligo are the three most prevalent forms of cutaneous irAE. ***Case Presentation:*** Here, we report a rare case of a pityriasis lichenoides et varioliformis acuta (PLEVA) that developed during pembrolizumab treatment for invasive bladder cancer. A 53-year-old man, receiving pembrolizumab for invasive bladder cancer, developed erythematous papules on his legs after his 11th infusion. The skin lesions gradually spread to his entire trunk and extremities. A punch biopsy revealed several apoptotic keratinocytes and spongiosis, along with perivascular and lichenoid lymphocytic infiltration with vacuolar alteration. Immunohistochemistry showed infiltration of CD4+ and CD8+ T cells in both the epidermis and dermis. Granzyme B-positive inflammatory cells were also slightly present. From these results, he was diagnosed with PLEVA, which might be classified as a lichenoid eruption, especially based on the histological findings. ***Conclusion:*** We hypothesize that the anti-PD-1 antibody might lead to epidermal necrosis by amplifying the expression of cytolytic molecules such as granzyme B in CD8+ T cells.

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Introduction

Anti-PD-1 immunotherapies, such as nivolumab and pembrolizumab, enhance T-cell responses against tumor cells by blocking the interaction between PD-1 and its ligand, PD-L1. While these therapies offer significant benefits in treating various malignancies, they can also lead to severe immune-related adverse events (irAEs), most notably those manifesting in the skin [1]. A previous study reported that 49% of patients with metastatic melanoma treated with anti-PD-1 antibodies developed a form of cutaneous irAE. The three most prevalent phenotypes were lichenoid reactions (17%), eczema (15%), and vitiligo (15%) [2]. In this context, we report a rare case of a pityriasis lichenoides et varioliformis acuta (PLEVA) that developed during pembrolizumab treatment for invasive bladder cancer. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

Case Report

A 53-year-old man, who had been receiving pembrolizumab at a dosage of 2 mg/kg every 3 weeks for invasive bladder cancer, developed itchy, erythematous papules on his legs, without a febrile condition, following his 11th infusion. Histological examination of the bladder cancer revealed urothelial carcinoma with a G3 malignancy grade and detected a Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation. The skin lesions progressively spread to his entire trunk and extremities. Some of these lesions evolved into purpuric papules and, within a month of their onset, were accompanied by pustules and crusted ulcers (Fig. 1a, b). A 4-mm trepan punch biopsy taken from an erythematous papule on his leg revealed acanthosis, parakeratosis, several apoptosis keratinocytes, and spongiosis. Additionally, perivascular and band-like lymphocytic infiltration, predominantly with vacuolar alteration of the basal layer, was evident (Fig. 2a, b). Immunohistochemistry showed infiltration of both CD4+ and CD8+ T cells in the epidermis and papillary dermis, with a predominance of CD8+ cells (Fig. 2c, d). Granzyme B-positive inflammatory cells were also slightly present (Fig. 2e). A blood test indicated an elevated C-reactive protein level at 2.54 mg/dL. Based on the clinical and histopathological findings, particularly the characteristic necrosis, he was diagnosed with PLEVA. Despite the discontinuation of pembrolizumab and the initiation of topical corticosteroids, the purpuric papules increased. Approximately 2 weeks after starting oral prednisolone (10 mg/day), the skin rash and itching gradually improved (Fig. 3a, b). Due to concerns about a repause of cutaneous manifestations, pembrolizumab treatment was discontinued.

Discussion

In patients undergoing anti-PD-1 therapy, lichenoid eruptions are the most common cutaneous irAEs, typically manifesting later in the treatment course [2]. Recent studies have suggested that the development of lichenoid eruptions may correlate with improved tumor responses [3]. The clinical presentation of lichenoid eruptions varies, ranging from classic lichen planus (LP) with its flat-topped violaceous papules to a morbilliform eruption and, rarely, pustules. Lichenoid eruptions often affect the trunk and extremities, with infrequent involvement of the palms, soles, and genitalia [4]. The most characteristic histological manifestation of a lichenoid eruption is a subepidermal band-like infiltration of cytotoxic lymphocytes and apoptosis of basal keratinocytes.

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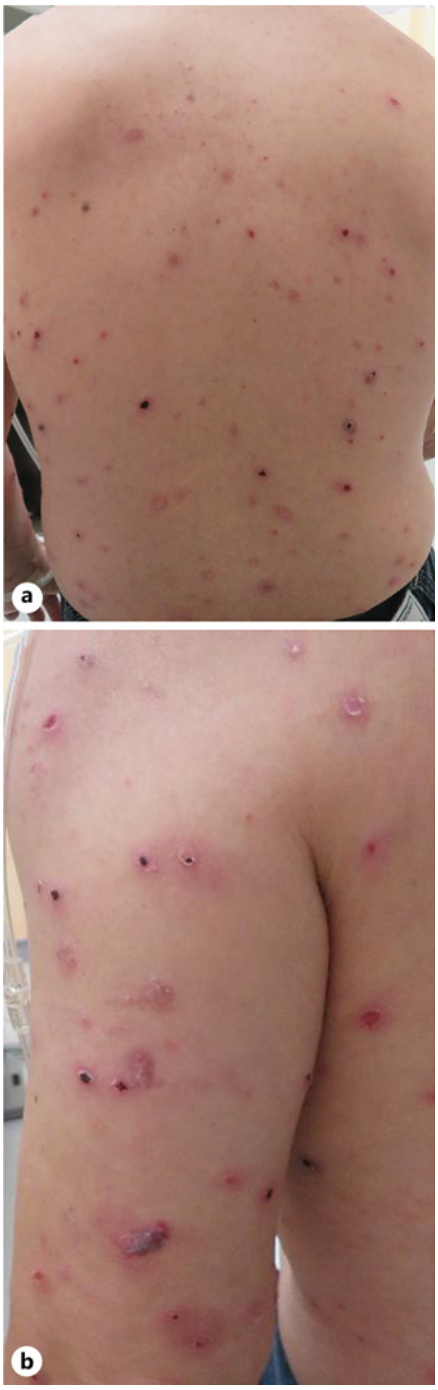

Fig. 1. Clinical features of this patient at the first visit. Erythematous lesions are evident on the trunk (**a**) and the upper thighs (**b**), some of which have central crusting and ulcers.

PLEVA is an uncommon cutaneous inflammatory rash characterized by diffuse red-brown papules at various stages, with scales. The papules may progress to form vesicles, pustules, and ulcers. While the diagnosis of PLEVA is primarily clinical, histological evaluation of lesional skin is crucial, revealing spongiosis, dyskeratosis, parakeratosis, acanthosis, and necrosis in the epidermis. Dermal findings include a wedge-shaped lymphohistiocytic inflammatory infiltrate, subepidermal vesicles, and perivascular lymphocytic infiltration [5]. The clinical and histopathological findings of lichenoid eruptions are diverse. Therefore, while our case was diagnosed as PLEVA, it was

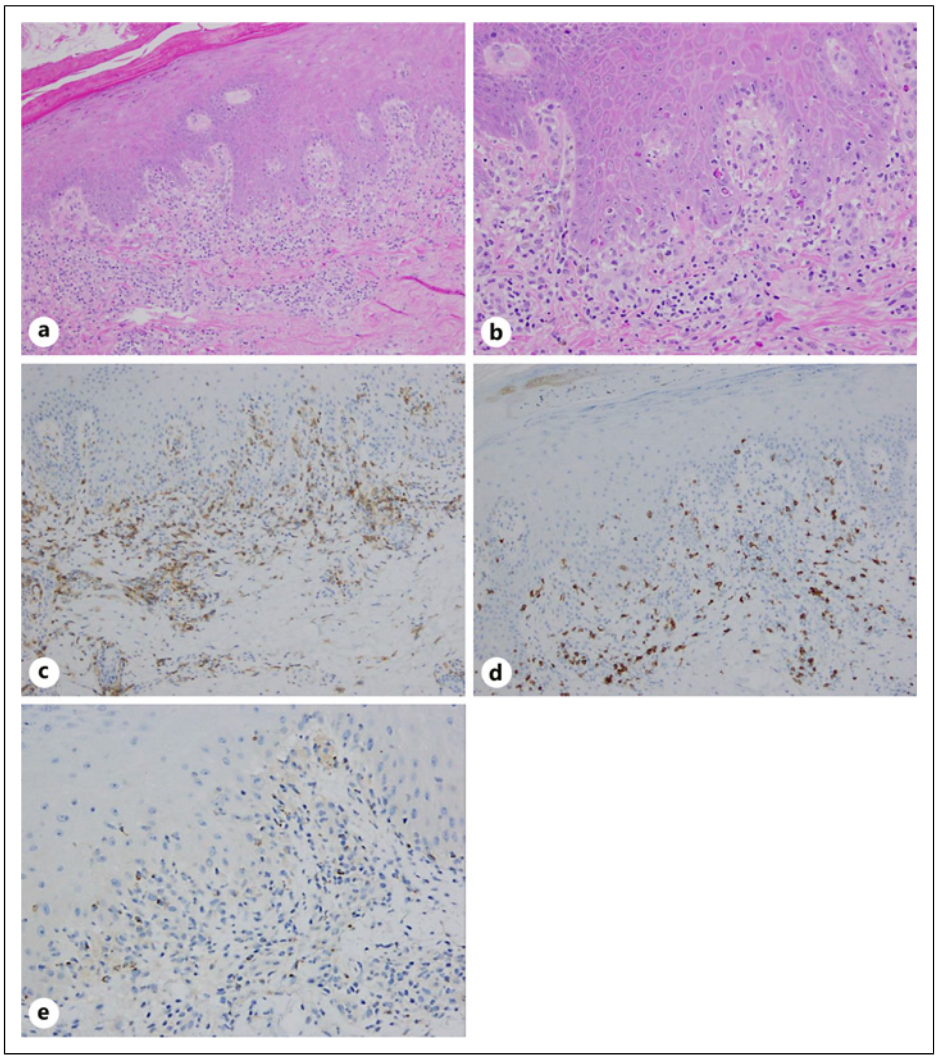

Fig. 2. **a**, **b** Histopathological findings reveal acanthosis, parakeratosis, scattered necrotic keratinocytes, and spongiosis. There is also a perivascular and lichenoid infiltration that is predominantly lymphocytic, accompanied by vacuolar alteration of the basal layer. (**a**, **b** Hematoxylin-eosin stain; original magnifications: **a**, ×100; **b**, ×200.) Immunohistochemical staining for CD4 (**c**, original magnifications: ×100) and CD8 (**d**, original magnifications: ×100) indicates that primarily CD8+ cells have infiltrated the epidermis. A few granzyme B-positive inflammatory cells are present in both the epidermis and the papillary dermis. **e** Immunohistochemical staining for Granzyme B; original magnifications: ×400.

considered within the category of lichenoid eruptions, particularly considering the histological findings.

Lichenoid drug-induced eruption (LDE) shares clinical and histological similarities with LP. A recent study found that, in the LDE group, most inflammatory T cells were CD8-positive, and, uniquely within this group, there was a significant positive correlation between the number of inflammatory cells expressing granzyme B and the number of clusters of apoptotic keratinocytes, in contrast to the LP group [6]. These findings suggest that, in LDE, keratinocyte apoptosis is primarily associated with granzyme B-mediated cytotoxicity, unlike in LP. Additionally, another study proposed that nivolumab enhances antitumor immunity by activating CD8+ T cells through Th9 cells, which subsequently promotes the expression of

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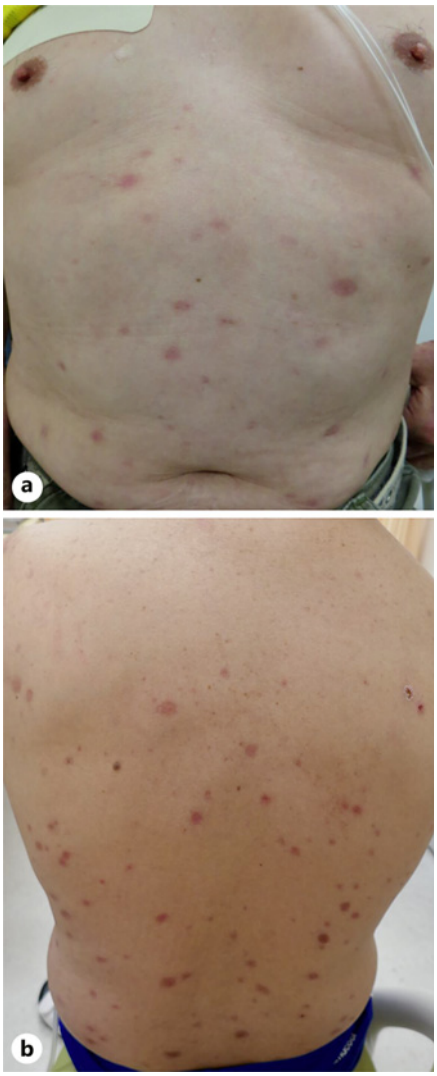

Fig. 3. a, **b** Clinical features of this patient 3 weeks after administration of oral prednisolone. Erythematous lesions are improved.

granzyme B and perforin in CD8+ T cells [7]. In our case, granzyme B-positive inflammatory cells were slightly present. We hypothesize that anti-PD-1 antibody might amplify IL-9 production, leading to epidermal necrosis by enhancing the expression of cytolytic molecules, such as granzyme B, in CD8+ T cells.

Sanlorenzo et al. [8] reported that 24 out of 83 (28.9%) patients treated with pembrolizumab developed morbilliform eruptions, most of which occurred after the first dose. Although these eruptions typically resolved with topical corticosteroids without necessitating the discontinuation of pembrolizumab, 2 patients (2.4%) required systemic corticosteroids (prednisone, 10–60 mg/day) and discontinued the pembrolizumab treatment. In a separate case, a single instance of PLEVA developed during pembrolizumab treatment, necessitating an increase in prednisolone dosage to 80 mg daily (1 mg/kg/day) to alleviate the cutaneous manifestations before ultimately discontinuing pembrolizumab [9]. Pharmacological therapy is generally not deemed necessary for PLEVA, though it may accelerate recovery and provide symptom relief. Treatment data for PLEVA are limited; however, various reports have identified systemic antibiotics and/or phototherapy as first-line therapies, often combined with corticosteroids [10]. In our case, the administration of oral prednisolone (10 mg/day), in addition to topical corticosteroids, was necessary. These reported cases suggest that PLEVA

developing during pembrolizumab treatment may require more intensive management than conventional PLEVA.

Although this report is a single case report and is limited in what it can provide, it presents the first case exploring the histological characteristics of PLEVA as an irAE. Our findings may offer deeper insights into the pathogenesis of cutaneous irAEs resulting from anti-PD-1 immunotherapies.

Statement of Ethics

The patient has given informed consent and the study was done according to the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

The data were collected and the initial manuscript was written by Yuki Mizutani. Keiichi Yamanaka assessed and edited the manuscript, offering valuable feedback and contributing to the final version. Ena Noda and Makoto Kondo provided medical treatment to the patient. Akinobu Hayashi contributed to histological analysis and diagnosis of the patient.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538767). Further inquiries can be directed to the corresponding author.

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